



Long-term outcomes of combined radiofrequency ablation and multipronged ethanol ablation for the treatment of unfavorable hepatocellular carcinoma

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PURPOSE

To evaluate the local efficacy, safety, and long-term outcomes of combined radiofrequency ablation (RFA) and multipronged ethanol ablation (EA) in the treatment of unfavorable hepatocellular carcinoma (HCC) and to determine the prognostic factors for survival.

METHODS

Between August 2009 and December 2017, 98 patients with 110 unfavorable HCC nodules who underwent combined RFA and multipronged EA were retrospectively enrolled in the study. Unfavorable HCC was defined as a medium (3.1–5.0 cm) or large (5.1–7.0 cm) HCC nodule, a tumor located at a high-risk site, or a perivascular tumor. The treatment response, overall survival (OS), and recurrence-free survival (RFS) were analyzed. The Kaplan–Meier method and Cox proportional hazards regression model were used to evaluate the prognostic factors.

RESULTS

Complete ablation was obtained in 80.9% (89/110) of the tumors after initial treatment. Major complications were observed in 3 (3.1%) patients. The cumulative incidence of local tumor progression (LTP) was 23.5% at five years, and no variable was found to be an independent predictive factor for LTP. The five-year OS and RFS rates were 41.9% and 34.0%, respectively. Multivariate analysis showed that the serum alpha-fetoprotein level, tumor size, presence of residual tumor after ablation, and extrahepatic metastases were significant prognostic factors for OS ($P = 0.023$, $P = 0.030$, $P = 0.001$, and $P = 0.010$, respectively). Tumor type and the number of tumors were predictive factors for RFS ($P = 0.029$ and $P = 0.001$, respectively). A perivascular tumor was not an independent predictive factor for OS or RFS.

CONCLUSION

Combined RFA and multipronged EA is a safe and effective treatment for unfavorable HCC, especially for perivascular tumors.

KEYWORDS

Combine, ethanol, hepatocellular carcinoma, radiofrequency ablation, survival

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Hepatocellular carcinoma (HCC) is the fifth most common cancer and a major cause of cancer-related death worldwide.^{1,2} Patients with early-stage HCC can be cured by therapies such as hepatic resection, liver transplantation, or ablation. Radiofrequency ablation (RFA) has recently become a treatment option for HCC.³

Despite the success of RFA treatment for small tumors, the local tumor complete ablation (CA) rates decline markedly for HCC tumors with a diameter >3 cm; meanwhile, the local tumor recurrence rate for RFA is higher than that for resection because RFA alone can only induce a limited volume of coagulated necrosis.⁴ A perivascular tumor location has been

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reported to be an independent predictive factor for local tumor progression (LTP) after RFA.⁵ This finding could be explained to some degree by the “heat-sink” effect, which is a well-known phenomenon that occurs when thermal energy disseminates from the treated lesion because of blood flow in the nearby blood vessels. This has an adverse impact on thermal ablation and induces tumor cells around the major intrahepatic vessels to escape from the thermal energy.

Some studies have shown that combined percutaneous RFA and ethanol ablation (EA) is an effective treatment for HCC in high-risk locations, which is defined as a tumor less than 0.5 cm from the gastrointestinal tract, gallbladder, diaphragm, or large bile duct (including hepatobiliary and bile ducts with a diameter >0.3 cm), a tumor located directly in contact with the liver capsule,^{6,8} a tumor near the large vasculature >0.3 cm, or a tumor near to the heart (perivascular tumor).^{9,10} A retractable multipronged injection needle was developed to overcome the limitations of the conventional EA technique.¹¹ The authors’ preliminary study confirms that medium (3.1–5.0 cm) and large (5.1–7.0 cm) HCC nodules can be treated effectively and safely with this combined ablation therapy.¹²

The aim of the current study is to evaluate the local efficacy, safety, and long-term outcomes of combined RFA and EA as a treatment for unfavorable HCC, especially perivascular tumors, and determine the prognostic survival factors. A multipronged injection needle (Quadra-Fuse; Rex Medical, Conshohocken, PA, USA) is used for EA. To the authors’ knowledge, no previous studies have reported long-term outcomes of combined RFA and EA with a multipronged injection needle.

Methods

An Institutional Review Board of the hospital approved this retrospective study with a

waiver of informed consent for participation in the study [ethical review decision/protocol number: 2012 (68)]. Before treatment, the authors obtained written informed consent from each patient.

Patients

Between August 2009 and December 2017, a total of 98 patients (86 men, 12 women; mean age 55.0 ± 12.7 years) with 110 unfavorable HCC nodules (4.0 ± 1.0 cm) who underwent combined RFA and multipronged EA were retrospectively enrolled in the study. In the current study, unfavorable HCC was defined as medium (3.1–5.0 cm) or large (5.1–7.0 cm) HCC tumors, a tumor located at a high-risk site, or perivascular tumors. The diagnosis of HCC was based on a biopsy or the non-invasive diagnostic criteria of the European Association for the Study of the Liver. The inclusion criteria were as follows: (a) adult patients with HCC or recurrent HCC who refused to undergo surgery; (b) single or multiple tumors (no more than three HCC tumors, with the largest lesion 7.0 cm in diameter) without extrahepatic metastasis or macrovascular invasion; (c) liver function classified as Child–Pugh class A or B; (d) platelet count $>50 \times 10^9/L$ and prothrombin time ratio $>50\%$; and (e) visualization of the HCC nodule at the planning ultrasonography examination for RFA. Patients with liver function classified as Child–Pugh class C, those with uncontrolled coagulopathy, or those with a history of ethanol allergy were excluded from the study.

Tumor diameters were determined as the largest dimension measured using B-mode ultrasound. Tumor numbers were determined from contrast-enhanced ultrasound (CEUS) with SonoVue as a contrast agent and contrast-enhanced computed tomography (CECT) findings. The Barcelona Clinic Liver Cancer (BCLC) staging and treatment strategy was used to make treatment decisions for stage 0–A patients. For BCLC stage B patients, treatment decisions were made based on the results of a multidisciplinary team (MDT). Diagnostic and treatment decisions were made in consensus by the MDT consisting of hepatobiliary surgeons and interventional radiologists.

Ethanol ablation

A multipronged injection needle was used to inject ethanol. This device included an 18-gauge 20 cm-long puncture needle consisting of an echogenic tip; three retractable tines, each with two evenly spaced

through-holes (four fluid exits); and a connector with extension tubing. With ultrasound guidance, the needle was introduced percutaneously into the tumor center, and the needle tip was positioned at the bottom of the target tumor. An injection–rotation–injection maneuver was used as described in our previous reports.^{12,13} The maximal extent of prong deployment was equal to the tumor’s largest diameter. Ethanol was injected until the whole tumor appeared completely hyperechoic. The amount of ethanol was calculated according to the tumor size and was kept between one-quarter and one-third of the estimated tumor volume. During any necessary pause of ethanol injection, 0.5–1.0 mL of heparinized saline solution was injected to prevent thrombosis inside the prongs. After the completion of the injection, the needle was left in the tumor for 1–2 min to prevent possible ethanol reflux before it was removed.

Radiofrequency ablation

We used the RITA Medical System (RITA Medical System, Mountain View, CA) and the Cool-tip TM RFA System (Cool-tip System, Covidien, Mansfield, MA). The combined ablation procedure was the same as that described in the authors’ previous report for tumors located or not located at high-risk sites.^{12,13} For tumors located at high-risk sites, the Cool-tip System was used. For tumors not located at high-risk sites, the RITA Medical System was used. RFA was performed 3–5 min after EA following the manufacturer’s guidelines. During the ablation, the authors tried to obtain an adequate coagulation volume with a sufficient safety margin of 0.5 cm. CEUS was performed approximately 30 min after ablation, providing an initial evaluation of the treatment effect. Additional treatment was performed if any tumor residue was found.

Assessment of treatment response and follow-up

All complications related to thermal ablation were categorized according to the grading system of the Society of Interventional Radiology.¹⁴

The initial CA evaluation performed one month after ablation was assessed using CECT and CEUS simultaneously. All patients were scanned using a 64-slice helical CT scanner (Toshiba, Tokyo, Japan) with the following parameters: 0.5 mm \times 64 mm collima-

Main points

- Combined radiofrequency ablation (RFA) and multipronged ethanol ablation (EA) is a safe and effective modality for treating unfavorable hepatocellular carcinoma.
- Combined RFA and multipronged EA expand the indication of thermal ablation to tumors of 5 cm in diameter.
- A high serum alpha-fetoprotein level, large tumors, residual tumors after ablation, and extrahepatic metastases have a significant negative effect on overall survival.

Complications

No ablation-related deaths occurred in the current study. Three patients (3.1%) experienced major complications. One patient suffered from intra-abdominal hemorrhage and remained hospitalized for 27 days after the ablation procedure. This patient initially presented with abdominal pain, then developed an abdominal infection, and was diagnosed with spontaneous peritonitis, which was successfully treated with ultrasound-guided ascites drainage and antibiotics. Another patient developed acute cholecystitis, which resulted in an eight-day hospital stay after treatment. This patient had a history of gallstones, which were successfully treated. The third patient had a tumor seeding in the abdominal wall at 21.4 months after treatment, and this tumor was successfully treated with RFA.

Ablation-related minor complications occurred in 3 patients (3.1%), including 2 cases of pleural effusion and 1 case of portal venous thrombosis that required no medical intervention.

Local tumor progression

Of the 98 completely ablated tumors, 23 (23.5%) lesions in 23 patients exhibited LTP during the follow-up period of 3.2–98.4 months (median, 31.1 months), and the LTP time was 2.8–64.2 months (median, 12.2 months). The cumulative incidence of LTP was estimated to be 2.3%, 15.9%, and 23.5% at one, three, and five years, respectively. The LTP rate was 29.6% (8/27) for tumors with sizes 3 cm, 23.4% (15/64) for tumors with sizes of 3.1–5.0 cm, and 0% (0/7) for tumors with sizes of 5.1–7.0 cm ($P = 0.332$). Among the 17 examined variables, including sex (male), age (>65 years), Child–Pugh class (A/B), hepatitis B/C virus status (+/–), serum alanine aminotransferase level (>40 U/L), serum total bilirubin level (>17.1 $\mu\text{mol/L}$), serum albumin level (>35 g/L), prothrombin time (>14 s), platelet count (>100 $\times 10^9/\text{L}$), serum AFP level (<20 ng/mL/20–200 ng/mL >200 ng/mL), tumor type (primary/recurrent), number of tumors (single/multiple), tumor size (3 cm/3.1–5.0 cm/5.1–7.0 cm), tumor location (located at high-risk sites, perivascular), ethanol volume (>14.4 mL), and ablation time (>24 min), no variable was found to be a predictive factor for LTP. Among the 23 patients with LTP, 14 were treated successfully with repeated RFA, 1 was treated with TACE, 1 underwent liver transplantation, and 1 underwent hepatic resection. The remaining 6 patients also had distant multinodular recurrences that were treated with sorafenib.

Distant recurrence

Distant recurrence included IDR and extrahepatic metastases. Seventy (71.4%) of the 98 patients had IDR, which was identified 3.0–65.1 months after ablation (median, 8.0 months), during the follow-up period, including 19 patients with IDR in the left lobe of the liver, 34 patients with IDR in the right lobe of the liver, and 17 patients with IDR in the whole liver. In addition, 2 patients developed a portal vein tumor thrombus, which occurred after 2.2 months in one patient and after 3 months in the other patient. During the follow-up period, extrahepatic metastases, which were identified 3.0–55.5 months after ablation (median, 7.2 months), developed in 20 (20.4%) of the 98 patients, and the locations of the initial extrahepatic metastases were as follows: the lungs ($n = 9$), lymph nodes ($n = 6$), abdominal wall ($n = 2$), bone ($n = 1$), adrenal gland ($n = 1$), and spleen ($n = 1$).

Survival analysis

Overall survival

During the follow-up period, 53 (54.1%) patients died after ablation. The median survival time of patients who died after the procedure was 21.2 months, and the minimum and maximum survival times were 5.1 and 81.3 months, respectively. The interquartile range was 22.2 months. Among the patients who died, 37 (69.8%) deaths were related to HCC progression; 14 (26.4%) were attributed to cirrhosis-related complications, such as variceal bleeding and liver failure; and 2 (3.8%) involved causes unrelated to liver dis-

ease (e.g., one patient had pneumonia, and the other had a stroke). Six (6.1%) patients underwent liver transplantation 4.2–77.5 months after ablation (median, 6.3 months). The reasons for liver transplantation were HCC recurrence in 5 patients and liver failure in 1 patient.

The estimated one-, three-, and five-year OS rates after RFA were 87.3%, 54.3%, and 41.9%, respectively (Figure 1). In the multivariate analysis, the serum AFP level ($P = 0.023$), tumor size ($P = 0.030$), residual tumor ($P = 0.001$), and extrahepatic metastases ($P = 0.010$) were significant independent predictive factors for OS (Table 2).

Recurrence-free survival

The estimated one-, three-, and five-year RFS rates were 63.1%, 46.9%, and 34.0%, respectively. Estimates of the mean and median RFS were 42.8 months [95% confidence interval (CI): 33.0–52.6] and 31.9 months (95% CI: 11.8–52.0), respectively. In the multivariate analysis, tumor type ($P = 0.029$) and the number of tumors ($P = 0.001$) were significant independent predictive factors for RFS (Table 3).

Table 4 shows the local efficacy and long-term outcome of different tumor and patient types.

Discussion

One procedure of one radiofrequency electrode produces a necrotic zone of 3.0–5.0 cm in diameter. The form and size of the ablation area may be errant because of the heat-

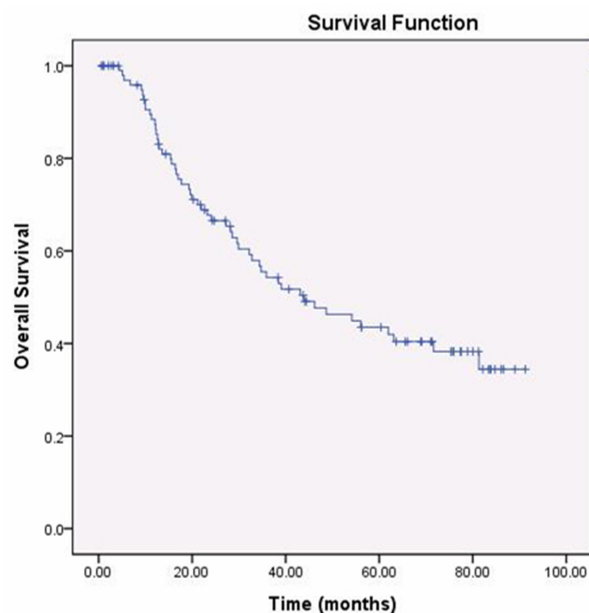


Figure 1. A graph showing Kaplan–Meier overall survival estimation for 98 patients who underwent combined radiofrequency ablation and multipronged ethanol ablation for hepatocellular carcinoma.

Table 3. Cox survival analysis of predictors for RFS in 86 patients with 98 HCCs after combined RFA and multipronged EA

Characteristic	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Gender (male)	0.532	0.164–1.723	0.293	-	-	-
Age (>65 years)	0.719	0.365–1.419	0.342	-	-	-
Hepatitis B/C virus (+/-)	0.938	0.332–2.649	0.903	-	-	-
Child–Pugh class (A/B)	0.650	0.198–2.132	0.478	-	-	-
Serum alanine aminotransferase level (>40 U/L)	0.910	0.490–1.691	0.767	-	-	-
Serum total bilirubin (>17.1 umol/L)	1.325	0.666–2.634	0.423	-	-	-
Serum albumin (>35 g/L)	0.960	0.445–2.072	0.917	-	-	-
Prothrombin time (>14 s)	1.187	0.423–3.335	0.745	-	-	-
Platelet count (>100×10 ⁹ /L)	1.199	0.589–2.440	0.617	-	-	-
Serum alpha-fetoprotein level (ng/mL)			0.053	-	-	0.117
20 vs. 20–200	1.359	0.594–3.107	0.468	1.437	0.607–3.403	0.410
20 vs. >200	2.282	1.170–4.453	0.016	2.098	1.038–4.240	0.039
Tumor type (primary/recurrent)	0.442	0.238–0.823	0.010	0.488	0.257–0.928	0.029
Number of tumors (single/multiple)	0.264	0.143–0.489	<0.001	0.338	0.177–0.646	0.001
Tumor size (cm)			0.001	-	-	0.053
3.0 vs. 3.1–5.0	1.191	0.563–2.519	0.648	1.498	0.698–3.217	0.300
3.0 vs. 5.1–7.0	7.217	2.292–22.724	0.001	4.809	1.482–15.600	0.009
Tumor location						
Located at high-risk sites (yes/no)	1.044	0.765–1.423	0.787	-	-	-
Perivascular (yes/no)	0.930	0.690–1.255	0.637	-	-	-
Ethanol volume (>14.4 mL)	0.942	0.698–1.271	0.695	-	-	-
Ablation time (>24 min)	0.990	0.522–1.879	0.975	-	-	-
LTP (yes/no)	1.074	0.741–1.556	0.707	-	-	-

P value of the Cox proportional hazards regression model <0.001. CA, complete ablation; CI, confidence interval; EA, ethanol ablation; HCC, hepatocellular carcinoma; HR, hazard ratio; RFA, radiofrequency ablation; RFS, recurrence-free survival; LTP, local tumor progression.

Table 4. Local efficacy and long-term outcome of different tumor and patient type

Tumor type	CA	LTP	Patient type	3-year OS	5-year OS	3-year RFS	5-year RFS
Medium tumor	57/69	15/64	Patients with medium tumor	0.564	0.634	0.464	-
Large tumor	6/13	0/7	Patients with large tumor	0.091	0	0	0
Tumor in high-risk locations	70/80	11/70	Patients with tumor in high-risk locations	0.335	0.531	0.429	-
Perivascular tumor	45/50	14/45	Patients with perivascular tumor	0.516	0.570	0.490	-

CA, complete ablation; LTP, local tumor progression; OS, overall survival; RFS, recurrence-free survival.

the combined ablation procedure used in the current study or were reported by other literature.^{9,12} Tumors located at high-risk sites or perivascularly were generally successfully treated without complications in the current study (Figures 2, 3), which indicates the minimal invasiveness of this combined therapy. The complication rates of patients with and without perivascular tumors were similar (3/58 vs. 3/52, respectively, $P = 1.000$).

The LTP rate was 23.5% in the current study. This rate is similar to the rates observed in other studies of combined RFA and EA treatment for HCC, which have been reported to be approximately 12.5%–32.6%.^{9,10,12,20} Some studies have reported that factors such as tumor size and perivas-

cular tumor location were predisposing factors for LTP.^{23,28} However, no such factor was found in the current study. The LTP rates of the patients with and without perivascular tumors were similar (14/58 vs. 9/52, respectively, $P = 0.379$). Because HCC has a relatively high tendency to exhibit intrahepatic vascular invasion, the current study implies that RFA and EA combination therapy is useful for preventing LTP in patients with perivascular tumors. The LTP rate is highest for small tumors and decreases with increasing tumor diameter, which occurs because many large tumors are not completely ablated during the initial treatment.

In recent years, TACE, followed by RFA, has been more widely applied in clinical settings

because TACE can reduce the heat-sink effect of blood flow by lessening hepatic arterial flow. The five-year OS of TACE and RFA has been reported to be approximately 31.0%–46.0%,²⁹ which was similar to the current data of our study (41.9%). Our results showed that the significant predictive factors for poor OS were a high serum AFP level, tumor size, residual tumor after ablation, and extrahepatic metastases. Tumor size as a predictive factor for OS has been reported in many previous studies.^{22,30–32} A high serum AFP level is usually related to tumors with a higher degree of malignancy and is predictive of a high rate of HCC recurrence and poor prognosis after percutaneous ablation. Residual tumor after ablation indicates treatment failure; there-

- may achieve comparable long-term outcomes in larger hepatocellular carcinoma (3.1-4 cm) and in high-risk locations. *Kaohsiung J Med Sci.* 2014;30(8):396-401. [\[CrossRef\]](#)
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